Microalbuminuria in pregnancy as a predictor of preeclampsia and eclampsia

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Summary

***Introduction*: Hypertensive disorders of pregnancy are common major complications of pregnancy and are responsible for significant morbidity and mortality in the fetus, the newborn infant and the mother.**

***Objectives:* To access if a single estimation of urinary microalbumin at booking would be of value in the prediction of subsequent development of preeclampsia or eclampsia**

***Methods*: We studied at booking urinary microalbumin excretion in one hundred healthy normotensive Nigerian pregnant women attending the antenatal clinic and followed them till delivery. The women were grouped into 3 i.e. those with normal, micro and macro albumin excretion during analysis.**

***Results*: Ninety-three of these patients delivered at UCII, 2 had spontaneous abortions and five delivered elsewhere. At booking, 57 patients (61.3%) had normal albumin excretion and 22 (23.7%) and 14(15%) had microalbuminuria and gross albuminuria respectively. The men urinary albumin excretions for the normal, micro and gross albuminuria groups were 10.2 ± 8.4, 67.0 ± 55.2 and 321.4 ± 14.0mg/24 hours respectively. There was increased incidence of preeclampsia with an increase in albumin excretion and this was statistically significant (P value <0.05). No patient developed eclampsia. With single urinary microalbumin excretion estimation at booking, the sensitivity, specificity, positive and negative predictive values of albuminuria were 88.9%, 67.9%, 22.2% and 98.3% respectively.**

***Conclusion*: Urinary microalbumin excretion when used as a single test at booking appeared to predict preeclampsia with a high sensitivity but a low positive predictive value.**

Keywords: ***Albuminuria, Pregnancy, Predictor, Pre-eclampsia, Eclampsia.***

Résumé

Introduction: Les troubles hypertensifs de la grossesse sont des complications principales très fréquentes pendant la grossesse et ils sont responsables de la morbidité et la mortalité importante dans le foetus, nouveau-né et chez la mère.

*Objectifs:*Evaluer si une estimation simple de la microalbuminurie, tout en regardant, pourrait avoir la valeur dans la prédiction du dévéloppement ultérieur de la prééclampsie ou de l'éclampsie.

Méthodes: Nous avons étudié, à l'inscription, l'excrétion microalbumine urinaire chez cent femmes enceintes normotensives nigérianes en bonne santé qui fréquentent la clinique antinatale et nous les avons suivi jusqu'au moment de l'accouchement. Les femmes étaient en groupes de 3 c-à-d celles qui sont normales, micro et excretion macro albumine au cours de l'analyse.

Résultats: Quatre vingt trieze de ces patients ont accouché à l'UCH, 2 avaient des avortements spontanés et les autres cinq ont accouché ailleurs. Au cours de l'inscription, 57 patientes soit 61,3% avaient une excrition albumine normale et 22 soit 23,7% et 14 soit 15% avaient la microalbuminurie et une grave albuminurie respectivement. Les excretions albumines urinaire moyennes pour les groupes normaux, micro et grave albuminuries étaient 10,2±8,4; 67,0±55,2 et 321,4 ±14,0mg/24 heures respectivement. On avait noté une augmentation de la prééclampsie avec une augmentation de l'excretion albumine et ceci était statisquement significatif. (P-valeur <0,05). Aucune patiente était atteinte de l'éclapsie. Avec une estimation de l'excretion microalbumine simple au cours de l'inscription, la sensitivité, spécificité valeurs prédictives positives et négatives de l'albuminurie étaient 88,9%, 67,9%, 22,2^ et 98,3% respectivement.

Conclusion: L'excretion microalbumine urinaire quand utilisée comme un test simple pendant l'inscription parait prédire une prééclampsie avec une sensitivité très élevée mais une valuer prédictive positive basse.

Introduction

Hypertensive disorders of pregnancy are common and are major complications of pregnancy. They are responsible for significant morbidity and mortality in the fetus, newborn infant and mother [1,2,3]. Preeclampsia/eclampsia occurs in up to 10% of all pregnancies[4]. Preeclampsia describes a common syndrome that occurs in the second half of pregnancy and often manifesting with hypertension and protenuria[5]. It is the second leading cause of maternal mortality worldwide, constituting 12 - 18% of pregnancy related maternal deaths[6]. Black women have as much as twice the relative risk of developing it than whites[6]. In the more severe forms, patients may develop seizures and coma (eclampsia). It has been postulated that abnormal placentation believed to be due to failure of the second wave of trophoblastic invasion of the spiral arteries from the 20th week of pregnancy is the primary insult[7,8]. The signs and symptoms of preeclampsia become apparent at a relatively late stage in pregnancy, usu-

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ally in the third trimester. However, the underlying causes of the pathophysiologic mechanisms that are thought to be responsible for the disease process appears to occur much earlier in pregnancy[9]. For this reason, it seems logical to search for earlier indicators for the disorder. More than 100 clinical, biophysical and biochemical tests have been reported in the world literature to predict the development of preeclampsia[10]. Proteinuria has classically been an important finding in the diagnosis of preeclampsia/eclampsia. However, customary dipstick methods for detecting protenuria fail to detect minimal elevation in urinary excretion of albumin that may be present before other clinical signs and symptoms of preeclampsia. With radioimmunoassay and other sensitive methodology for detection of microalbuminuria, it is now possible to detect minimal elevations in albumin excretion that have gone unnoticed in the past. Microalbuminuria refers to sub-clinical elevation of urinary albumin excretion[11]. It has been shown to precede the development of chronic renal failure in patients with insulin-dependent diabetes mellitus[12], and may be evidence of renal involvement in hypertension. Healthy pregnant women may not excrete albumin in amounts detectable by the conventional dipsticks screening test. The presence of microalbuminuria should be an important clinical finding in pregnant women.

The purpose of this study therefore, was to assess the relationship between urinary albumin excretion, hypertension in pregnancy and preeclampsia/eclampsia early at booking.

Materials and methods

This study was performed at the University College Hospital (UCH), Ibadan, Nigeria. It was conducted within 15-months period. The Joint Ethical Committee of the University of Ibadan/University College Hospital, Ibadan approved the study protocol.

One hundred healthy normotensive Nigerian pregnant women attending the antenatal clinic for the first time for booking were recruited into the study. Patients that were excluded were those with a history of significant liver disease, overt renal disease and urinary tract infection. Subjects were further excluded from the final analysis if they failed to come for at least two routine antenatal visits or did not deliver in U.C.H after being recruited. The patients were adequately counselled and their informed consent obtained before they were included in the study.

At booking a complete clinical history was obtained from each patient with emphasis on her age, parity, last menstrual period, past obstetric and medical history as well as drug history. The family, social history and the history of the present pregnancy were also obtained. Patients were asked about symptoms of a vaginal or urinary tract infection. This was then followed by a complete physical examination including their blood pressure. The blood pressure was calculated as the average of two determinations carried out after fifteen minutes rest and at one minute intervals in the sitting position using a standard mercury sphygmomanometer and an appropriate sized cuff placed at the heart level. The cuff was rapidly inflated to 30mmHg above the estimated systolic blood pressure as detected by palpitation of the radial artery. The cuff was rapidly deflated and reinflated to this level and gradually deflated while listening with a stethoscope over the cubital fossa. The systolic blood pressure was taken as the level of pressure at which the Korotkoff's sounds were heard (Phase I) and the diastolic pressure as the level at which the sound became muffled (Phase IV). Blood pressure was considered to be normal if the measurement was less than 140/90mmHg at booking.

Mid-stream clean catch urine sample was collected in a clean sterile universal bottle. The urine sample was immediately tested for protein using multistix reagent strips (Bayer Diagnostic Division, U.S.A), which has a detection limit of greater than 0.3 g/dl (1+). The result was reported as negative, trace, 1+, 2+, 3+ or 4+. Microscopy was done to exclude urinary tract infection (U.T.I), and greater than 5 white blood cells per high power field was regarded as significant. Samples found to be negative for albumin and UTI were then stored at 4°C until batch analysis for microalbuminuria and creatinine was done within 8 weeks of collection. Earlier on the patients were given explicit verbal and written instructions regarding the 24-hour urine collection. The collection was to start at 8.a.m the following day and completed 24 hours after, using the clear white plastic 4 litre container that was given to the patients and returned to the clinic immediately after collection. Subjects were asked to recapitulate this procedure. Patients with incomplete collection were made to repeat it.

All women were instructed to adhere to their normal diet and physical activity. The volume of urine was measured and two aliquots were stored for future assay. One was frozen at minus 20°C for creatinine and the other kept at 4°C for albumin assays respectively. All albumin assays were performed using the Turbidimetry method[13]. All urine specimens were run in duplicate in the same assay with the mean value used for analysis.

The patients were followed up till delivery, receiving routine antenatal care. Normal albuminuria was defined as albumin excretion <30mg/24 hours , microalbuminuria as between 30–300mg/24 hours and macro albuminuria as >300mg/24 hours[14]. At each visit, the blood pressure was measured and urine tested for albumin. Urine culture and sensitivity tests were performed when necessary to exclude urinary tract infection as a cause of proteinuria.

The presence of preeclampsia was defined as the presence of a blood pressure of 140/90mmHg or more, or a rise of 30mmHg in systolic pressure, or of 15mHg in diastolic pressure (measured twice, 6 hours apart at bed rest) associated with protenuria. Eclampsia was defined as occurrence of seizures not attributable to other causes in a preeclamptic patient.[15].

All the data obtained were coded and keyed into a computer using the EPI-INFO version 6 programme for analysis. Statistical analyses for categorical variables were based on the Chi-square tests whereas continuous variables were based on the Kruskal Wallis test and analysis of variance (ANOVA) for repeated measurements. Results were expressed as means ± SD except where otherwise stated. A P-value of <0.05 was considered statistically significant (providing a 95% confidence interval).

Results

One hundred Nigerian normotensive patients were recruited into the study at booking and were followed up till delivery. Ninety-three of them delivered at UCH, 2 had spontaneous abortions at 18th and 20th weeks respectively and 5-delivered elsewhere. The patients were grouped into 3, those with normal, micro and gross albumin excretion to determine the relationship of albuminuria with the outcome of pregnancy and the development of hypertension in pregnancy, preeclampsia and eclampsia.

At booking, 57(61.3%) had normal urinary albumin excretion with a mean of 10.2 ± 8.4mg/24hr and 22(23.7%) had microalbuminuria (67.0±55.2mg/24hr) and 14(15%) of them had macro albuminuria with a mean of 321.4±14.0mg.24hr although

Table 1 Age and parity distribution of 93 patients followed till delivery

	Normal (N = 57)		Micro Albuminuria (N = 22)		Macro Albuminuria (N = 14)		Total (N = 93)	
Age (Years)	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
≤ 20	1	1.8	0	0	1	7.1	2	2.2
21 – 25	6	10.5	2	9.1	2	14.3	10	10.7
26 – 30	27	47.4	9	40.9	6	42.9	42	45.2
31 – 35	18	31.6	5	22.7	4	28.6	27	29
>35	5	8.7	6	27.3	1	7.1	12	12.9
Total	57	100	22	100	14	100	93	100
Parity								
0	25	43.9	6	27.3	5	35.7	36	38.7
1 – 2	24	42.1	9	40.9	8	57.1	41	44.1
3 – 4	7	12.3	6	27.3	1	7.2	14	15.1
≥5	1	1.7	1	4.5	0	0	2	2.1
Total	57	100	22	100	14	100	93	100

P value for age = >0.05 (NS)
P value for parity = <0.05 (S)

the patients were negative to dipsticks at booking. Of the 7 patients that did not complete the study, 3 belonged to the normal albuminuria group and 4 to the macro albuminuria group. Table 1 shows the age and parity distribution of the patients. The mean ages for the normal, microalbuminuric and macro albuminuric patients were 29.58 ± 4.32, 31.49±4.72 and 29.74 ±4.64 years respectively. There was no statistically significant difference between the mean ages of those with albuminuria and those without, P value >0.05. The mean parity for the patients with normal, micro and macro albumin excretions were 1.0, 1.7 and 1.0 respectively with a range of 0 to 5, 0 to 5 and 0 to 3 respectively. This was statistically significant with a P value < 0.05.

Table 2 shows the mean blood pressures of the subjects at booking and at delivery. The mean (SD) systolic, diastolic and mean arterial blood pressure at booking and delivery were similar in all the 3 groups. There was no statistically significant difference in any of these values P>0.05. Table 3 describes the relationship between urinary albumin excretion and mean gestational age at booking/delivery, mode of delivery, mean birth weight and fetal outcome. The overall mean gestational age at booking was 23.1 weeks and at delivery was 38.3weeks. The mean gestational ages at booking in the 3 groups were 22.3 weeks (range 9 – 39), 22.5 weeks (range 10 – 38) and 26.2 weeks (range 12 – 38) for the normal, micro and macro albuminuric patients respectively, while the mean gestational age at delivery

Table 2 Mean systolic, diastolic and arterial blood pressures at booking and delivery

	Normal (N = 57)	Micro Albuminuria (N = 22)	Macro Albuminuria (N = 14)	P Value
Mean systolic blood pressure at booking (mmHg)	113.2 ± 9.7	115.2 ±13.8	117.5 ± 16.0	>0.05 (NS)
Mean diastolic blood pressure at booking (mmHg)	68.6 ± 8.3	71.9 ±11.1	70.8 ± 11.4	>0.05 (NS)
Mean arterial blood pressure at booking (mmHg)	83.4 ± 7.8	86.3± 11.4	86.4 ± 12.4	>0.05 (NS)
Mean systolic blood pressure at delivery (mmHg)	120.4 ± 13.7	119 ± 13.1	128.6 ± 14.1	>0.05 (NS)
Mean diastolic blood pressure at delivery (mmHg)	74.8 ± 10.9	73.9 ± 9.9	81.4 ± 8.6	>0.05 (NS)
Mean arterial blood pressure at delivery (mmHg)	90.0 ± 10.8	89.0 ± 9.8	97.1 ± 9.4	0.05 (NS)

Table 3 Mean gestational age at booking and delivery, mode of delivery, mean birth weight and fetal outcome in 93 patients that delivered in UCH.

	Normal (N = 57)		Micro Albuminuria (N = 22)		Macro Albuminuria (N = 14)		P value
Mean gestational age at booking (weeks)	22.3± 6.4		22.5 ± 7.0		26.2 ± 7.9		<0.05 (S)
Mean gestational age at delivery (weeks)	38.5 ± 2.3		38.5 ± 1.7		37.1 ± 2.4		>0.05 (NS)
Mode of delivery	(N = 57) No	%	(N = 22) No	%	(N = 14) No	%	Total (N = 93) No %
– Spontaneous vaginal delivery	40	70.1	15	68.2	11	78.6	66 71
– Forceps delivery	2	3.5	1	4.5	0	0	3 3.2
– Emergency ceasarean section	14	24.6	6	27.3	2	14.3	22 23.7
– Elective casearean section	1	1.8	0	0	1	7.1	2 2.1
Mean birth weight (KGS)	3.06 ± 0.7		3.06 ±0.47		2.83 ± 0.7		P value = >0.05 (NS)

Table 4 Development of pregnancy induced hypertension, preeclampsia and eclampsia

	Normal (N = 57)		Micro Albuminuria (N = 22)		Macro Albuminuria (N = 14)		Total (N = 93)		P value
	No	%	No	%	No	%	No	%	
Pregnancy induced hypertension	3	5.3	2	9	0	0	5	5.4	
Preeclampsia	1	1.8	3	13.6	5	35.7	9	9.7	<0.05 (S)
Eclampsia	0	0	0	0	0	0	0	0	

Table 5 Predictive values of albumin at booking

	Albumin ≥30mg/24hr
Patients with preeclampsia	8
Patients with normal outcome (Normotensive)	28
Sensitivity (%)	88.9
Specificity (%)	67.9
Positive predictive value (%)	22.2
Negative predictive value (%)	98.3

was 38.5weeks (range 32 – 42), 38.5 weeks (range 34 – 41) and 37.1 weeks (range 32 – 42). The difference in the mean gestational ages at booking was statistically significant with a P value <0.05, but the gestational age at delivery was not, with a P value >0.05.

Spontaneous vaginal delivery occurred in 66(71 %) of all the patients. This occurred more in the albuminuric patients compared with the other group. Forceps delivery was the mode of delivery in 3(3.2%) of patients. The indications were poor maternal effort in the second stage of labour together with fetal distress. Caesareaan delivery occurred in the remaining 24 (25.8%). Caesarean section occurred more often in the albuminiric group. The indication for elective caesarean sections was 2 previous caesarean sections and the indications for emergency caesarean sections were fetal distress, failure to progress in labour and antepartum haemorrhage.

Ninety-one patients (97.8%) had live birth. The mean birth weights were 3.06 ±0.7, 3.06±0.47 and 2.83 ± 0.7kgs for the normal, micro and macro albuminuria patients respectively. This was not statistically significant with a P value >0.05. There was no maternal death in this study.

Table 4 described the frequency of hypertension in preg-

nancy, preeclampsia and eclampsia in the subjects. The incidence of preeclampsia was 9.7%. Of this, 88.9% had albuminuria while 11.1% had normal albumin excretion at booking. This was statistically significant with a P value <0.05. There was increased incidence of preeclampsia with an increase in albumin excretion. The incidence of pregnancy-induced hypertension was 5.4%, occurring in only 5 patients. Of this, 3 patients (60%) had normal albumin excretion and 2 patients (40%) had albuminuria. No patient developed eclampsia.

Table 5 shows the predictive value of albuminuria (30mg or more/24hr) at booking. Eight of the 36 patients with albuminuria developed preeclampsia in this study giving a sensitivity of 88.9%, while 57 of the patients who did not have albuminuria were among the 84 patients that did not develope preeclampsia giving a specificity of 67.9%.

Eight of the 36 patients with albuminuria developed preeclampsia giving a positive predictive value of 22.2%, while 56 patients out of 57 patients without albuminuria did not develope preeclampsia giving a negative predictive value of 98.3%.

Discussion

Minimally increased excretion of albumin is not generally measurable by the dipstick method, which is the conventional test ordinarily used to screen for albuminuria at booking in most antenatal clinics. Such slightly increased excretion of albumin has been shown to be predictive of the subsequent development of clinical nephropathy in insulin-dependent diabetic patients,[12] essential hypertension[16] and other cardiovascular diseases especially in the elderly[17]. Because albuminuria is one of the classic signs of preeclampsia, it has been hypothesized that the presence of microalbuminuria might be useful in predicting which patients develop preeclampsia/eclampsia. This study confirms that changes in urine albumin excretion are present in some otherwise symptom free patients in whom preeclampsia may eventually develop. Some of the subjects who were negative to dipsticks test also produced albumin in the macro albuminuria range, this may be related to the sensitivity of the test strip used. It has been found that the screening test for albumin may not sometime correspond to the 24hr albumin excretion[18]. Black women have been shown to have twice the relative risk of whites of developing preeclampsia[6]. In this study only 9.7% of the population developed preeclampsia, this was slightly above the generally accepted incidence of between 2 to 8% of pregnancies[19]. Pregnancy induced hypertension occurred in 5.4% of patients although 2 of them had microalbuminuria, they did not develop preeclampsia. No patient developed eclampsia. This may be a reflection of adequate care provided for the patients during the study.

Classically, preeclampsia is a disease of primigravid patients with at least two thirds of the cases occurring in this group[16]. Only 2 of 9 patients that developed preeclampsia were primigravid. Most patients that developed preeclampsia in this study were found to have albuminuria at booking in spite of the fact that they were negative to the test strip, this suggests that urine microalbumin excretion at booking may be used as a screening test in place of the present conventional test.

The sensitivity, specifically, positive and negative predictive values of urinary albumin excretion in the study were comparable to related studies in the past[20,21]. In this study the sensitivity and negative predictive value of a single estimation of urine microalbumin excretion at booking was high but the positive predictive value was rather low.

In conclusion about 15.1% of the patients in this study developed hypertensive diseases in pregnancy with 5.4% and 9.7% having pregnancy induced hypertension and preeclampsia respectively. Urinary albumin excretion when used as a single test was higher in those who later developed hypertensive diseases of pregnancy and had a high sensitivity in predicting preeclampsia but has a poor positive predictive value. In predicting preeclampsia/eclampsia, urinary microalbumin excretion may be a better option compared to the present conventional test.

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